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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,504	10/18/2000	Frederic DeSavage	P1748R1	6723

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EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 05/31/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/692,504

Applicant(s)

DESAUVAGE ET AL.

Examiner

Jessica H. Roark

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 March 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 6-10 and 14-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 11-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 October 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                    | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4-5</u> . | 6) <input type="checkbox"/> Other: _____                                    |

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### DETAILED ACTION

1. *Claims 1-34 are pending.*

2. Applicant's election of Group V (claims 1-5 in part and 11-13, as drawn to an antibody antagonist of TCCR) with a species election of IBD in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-10 and 14-34 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Since the elected species of a method of treating a Th1-mediated disease that is inflammatory bowel disease appears does not appear to be taught or suggested by the prior art, the search has been extended to encompass the additional species of Th1-mediated diseases.

*Claims 1-5 and 11-13 (as drawn to an antibody antagonist of TCCR) are under consideration in the instant application.*

3. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Provisional application 60/160,542 appears to provide adequate written support for the instant claims.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed*.

It is suggested that Applicant amend the Title to reflect the instantly recited methods.

6. Applicant's IDSs, filed 3/8/01 and 9/4/01 (Paper Nos. 4 and 5), are acknowledged.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Hyperlinks have been noted at least on page 18 at line 14 and page 21 at line 33.

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9. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.  
Please see the enclosed form PTO-948.

**INFORMATION ON HOW TO EFFECT DRAWING CHANGES**

**A. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

**B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

**Timing of Corrections**

*Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.*

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

11. Claims 1-5 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 11-13 are indefinite in that they utilize an arbitrary protein name, "TCCR". The instant recitation fails to distinctly claim what protein is antagonized. For example, others in the field may isolate the same protein and give it an entirely different name. Sprecher et al. (Biochem. Biophys. Res. Com. 1998; 246:82-90, IDS #57) describe proteins that share identical amino acid sequences as the instant human and mouse "TCCR" proteins, but name the proteins "WSX-1".

Applicant should particularly point out and distinctly claim the "TCCR" by claiming a sufficient number of characteristics associated with the protein (e.g. amino acid sequences).

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

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12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

13. It is noted that while the instant claims were limited by the restriction requirement to methods in which the "TCCR antagonist" is an antibody to TCCR; the breadth of the claims encompassing any "TCCR antagonist" is also addressed under 35 USC 112, first paragraph, in the rejections set forth below.

14. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite a "TCCR antagonist" as part of the invention.

However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of antagonizing a TCCR polypeptide. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3<sup>rd</sup> column).

Applicant does not appear to have reduced to practice any TCCR antagonists. Neither has Applicant provided a sufficient written description of any structure that may be correlated with the desired antagonistic function. A "TCCR antagonist" encompasses *any* molecule with the functional activity of stimulating the differentiation of T cells into a Th2 subtype, or treating a Th1-mediated disease. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed. In addition, as noted supra "TCCR" is an indefinite term and therefore the structure of a "TCCR" which is antagonized is also not described.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

While it is noted that the instant claims are drawn to methods, the claims nevertheless require an adequate written description of the "TCCR antagonist" employed in the methods.

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Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

15. Claims 1-5 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not appear to provide a sufficient enabling description of the instant methods of enhancing the differentiation of T-cells into the Th2 subtype, or of treating a Th1-mediated disorder.

The specification discloses that mice in which the gene encoding the TCCR polypeptide as set forth in SEQ ID NO:4 has been inactivated ("TCCR Knockout mice", Examples 1-2 on pages 86-88) demonstrate increased lymphocyte infiltration into the lungs compared to wild-type mice in a mouse model of asthma (example 3 on pages 89-91), have reduced production of immunoglobulin isotypes associated with Th1 responses in response to antigenic challenge (Example 12, pages 103-105), and have decreased ability to clear infections requiring a Th1 response (page 105). In addition, the specification discloses that T cells from TCCR knock out mice exhibit decreased Th1 and increased Th2 cytokine production in in vitro differentiation assays (page 105).

The state of the art recognized that it is unpredictable as to whether information derived solely from gene inactivation in mice is indicative that the protein inactivated is directly responsible for the observed phenotype.

Mak et al. (Nat. Rev. Immunol. 2001; 1:11-19) review that although gene-targeting has provided great insights into gene function, there are caveats that must be considered when assessing the phenotypes of genetically engineered mice (see entire reference, but especially the bridging paragraph of pages 13 and 14). In particular, Mak et al. note that engineered mutations in one gene can affect the expression of unaltered neighboring genes, giving rise to phenotypes that are unconnected to the gene of interest; and that gene deletions can also affect the architecture of an organ, such as the lymph nodes or spleen, which would have secondary effects on cells within these organs. Mak et al. conclude that there is a danger that such effects might be misinterpreted as primary effects of the gene mutation on the cells themselves.

Thus although the specification discloses that a genetic inactivation of TCCR in mice inhibits differentiation of T-cells into Th1 cells, as assessed by immunoglobulin isotype distribution and cytokine profiles, and that mice lacking TCCR have an increased lymphocytic infiltrate in a model of asthma; it is unpredictable if these phenotypes are due directly to inactivation of TCCR. Consequently, it would require undue experimentation of the skilled artisan to establish that the phenotype observed in the TCCR knockout mouse was a direct consequence of inactivation of the gene encoding TCCR, and in the absence of such objective evidence the application of TCCR antagonists in the instantly recited methods would be highly unpredictable.

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In addition, it is noted that the breadth of the antagonists encompassed by the instant claims is extensive. As noted supra, "TCCR" is an indefinite term, not limited to the polypeptides of SEQ ID NO:2 and SEQ ID NO:4. Further, even if a direct role of the TCCRs comprising SEQ ID NO:2 or SEQ ID NO:4 were established by sufficient objective evidence, the specification still would not provide a sufficiently enabling description of how to make and use a representative number of "TCCR antagonists" as currently recited in instant claims 1-5.

Although the specification sets forth generalized approaches for rational drug design and drug screening (Examples 10 and 11 on pages 101-103), the skilled artisan was well aware that the design of small molecule antagonists of cytokine receptors such as a TCCR was a formidable task. As noted by Proudfoot et al. (Immunol. Rev. 2000; 177:246-256), although small molecule antagonists have been produced for receptors of the chemotactic cytokines known as chemokines, no antagonists of cytokine receptors have yet been produced, despite intensive investigations (see especially comment bridging columns 1 and 2 on page 253).

Thus although the specification appears to provide sufficient guidance as to how to make certain antagonists of the TCCR polypeptides of SEQ ID NO:2 and SEQ ID NO:4, such as the antagonists antibodies recited in claims 11-13; it would require undue experimentation of the skilled artisan to make a representative number of "TCCR antagonists", as recited in instant claims 1-5.

In addition to the uncertainty associated with production of "TCCR antagonists", it would also be unpredictable as to whether a "TCCR antagonist" could be employed to accomplish the instantly recited methods, particularly *in vivo*.

It is again noted that instant claims 1-5 encompass a multitude of structurally diverse molecules. However, *in vivo* application of these various "TCCR antagonists" is fraught with technical difficulties, even were such antagonists developed. Pharmaceutical therapies in the absence of *in vivo* data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Given the technical difficulties associated with *in vivo* therapies, the limited guidance provided in the specification and the breadth of the claims encompassing any antagonist of any "TCCR"; the skilled artisan would be faced with undue experimentation in determining which "TCCR antagonists" could be utilized *in vivo*. Thus the skilled artisan would be forced to conduct undue experimentation to determine which, if any, antagonists of TCCR would function in the instant methods.

Finally, claims 3-5 and 11-13 recite methods of treating Th1-mediated diseases by administering a TCCR antagonist, including treating autoimmune inflammatory diseases, such as inflammatory bowel disease, and allograft rejection. Autoimmune inflammatory diseases that are Th1-mediated encompass a highly diverse group of diseases involving distinct pathophysiologies. However, as reviewed by O'Shea et al. (Nat. Rev. Immunol. 2002; 2:37-45) the state of the art recognized that the role of cytokines in regulating T-cell subtype for these diseases was extremely complicated: cytokines involved in determining T-cell subtype were known to be pleiotropic, exhibit functional redundancies, be involved in complex feedback loops, and to have both immunostimulatory and immunosuppressive activities (see especially pages 37-38).

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In addition to this complexity associated with cytokines and T-cell subtype, it is noted that for at least the autoimmune inflammatory disease insulin-dependent diabetes mellitus, treatment is in general limited to animals in which later development of the disease can be predicted. In humans, the immune system has already destroyed the beta cells which produce insulin by the time a patient presents with the symptoms of insulin-dependent diabetes mellitus. Thus in the absence of detailed protocols to detect the autoimmune inflammatory disease before beta cell destruction occurs, the specification does not appear to enable a method of treating insulin-dependent diabetes mellitus.

Thus data obtained solely from a TCCR knockout mouse model in which the polypeptide of SEQ ID NO:4 has been inactivated does not appear to provide sufficient guidance as to how a "TCCR antagonist" would function in a method of enhancing the differentiation of T-cells into the Th2 subtype, or of treating a Th1-mediated disorder in general, and human insulin-dependent diabetes mellitus in particular. No working examples are provided with respect to the ability of any antagonist in general, or a monoclonal antibody antagonist in particular, to produce modifications of T cell responses in mice in which the TCCR molecule is expressed. Further, no working examples are provided with respect to the effects of any antagonist of TCCR in general, or a monoclonal antibody antagonist of TCCR in particular, to mediate any effect with respect to human T cells. Finally, the specification does not appear to provide sufficient objective evidence that a "Th1-mediated disease", including inflammatory bowel disease, may be treated by administering any TCCR antagonist in general, or a monoclonal antibody antagonist of TCCR in particular.

Applicant is invited to provide sufficient objective evidence supporting that antagonists of TCCR, in particular monoclonal antibody antagonists, do function to enhance differentiation of T-cells into the Th2 subtype. Similarly, Applicant is invited to provide sufficient objective evidence that monoclonal antibody antagonists of TCCR inhibit one or more disease that is a "Th1-mediated disease".

However, given the unpredictability associated with the model and data disclosed; the experimentation left to one skilled in the art to practice the claimed invention is unnecessarily, and improperly, extensive and undue.

16. No claim is allowed.

17. The instant methods appear to be free of the prior art. Although the mouse and human TCCR polypeptides were known at the time the invention was made (e.g., U.S. Pat. No. 5,925,735), as were antibodies to them (e.g., U.S. Pat. No. 6,080,406) and the DNA encoding (e.g., U.S. Pat. No. 5,792,850); these references do not appear to teach or suggest that antagonists of TCCR could be used in methods of enhancing the differentiation of T-cells into the Th2 subtype, or that TCCR antagonists could be used in methods of treating Th1-mediated diseases.



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18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
May 29, 2002

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